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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,870	06/05/2000	Stephen C. Goshorn	690022.547	1301

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,870	GOSHORN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-22,24-32,37-39 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,24-32,37-39 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply; Exhibit I*.

DETAILED ACTION

1. The amendment filed July 17, 2004 is acknowledged and has been entered. Claims 33-36 have been canceled. Claims 18, 37, 39, and 65 have been amended.

2. Claims 18-22, 24-32, 37-39, and 65 are pending in the application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

3. Unless specifically reiterated below, Applicant's amendment filed July 17, 2004 has obviated the grounds of objection and rejection set forth in the previous Office action mailed December 17, 2003.

Response to Amendment

4. The amendment filed February 7, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is: "All prior applications are hereby incorporated herein by reference", wherein said prior applications are US Provisional Application No. 60/168,976, filed December 3, 1999, and US Provisional Application No. 60/137,900, filed June 7, 1999. An incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See 35 U.S.C. § 132(a). When a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference statement of the prior application. Therefore, the incorporation-by-reference statement in the amendment to the specification introduces new matter and renders the amendment improper. See *Dart Industries v. Banner*, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980). See 1268 OG 89 (18 March 2003).

Applicant is required to cancel the new matter in the reply to this Office Action.

Specification

5. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible disclosure appears in the specification at page 7, line 1.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference.

6. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequence "Gly_4-Ser" appearing in the specification at page 18 (line 28), page 20 (line 5), and page 37 (line 12) is not identified by a sequence identification number. Additionally, the sequences "$(Gly_4Ser)_3$" and "GSGSA" at page 30 (lines 9 and 15, respectively) are also not identified.

Applicant must provide appropriate amendments to the specification inserting the required sequence identifiers.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with a statement that the content of both copies are the same and, where applicable, include no new matter.

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of an improperly demarcated trademarks include BioFlo™ (page 35, line 4), Mazu™ (page 35, line 6), Powerfuge Pilot™ (page 35, line 19), Zorbax™ (page 36, line 15), and Dynamax™ (page 36, lines 17 and 18).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 25, 27, and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 25, 27, and 65 are drawn to the fusion protein, or a composition thereof, according to claim 18, wherein the antibody is "B9E9", or according to claim 26, wherein the single-chain Fv fragment is derived from antibody "B9E9".

It is noted that at page 31 (lines 9 and 10), the specification discloses that the hybridoma "B9E9-1D3" was acquired from BioProbe BV (Amstelveen, The Netherlands).

The "Catalog of Mouse Hybridomas" published on the Internet by BioProbe BV (Bandung, Indonesia) discloses the commercial availability of a hybridoma cell line having the laboratory designation "B9E9", which produces a monoclonal antibody that binds "CD20 V". However, because the specification discloses that a hybridoma designated "B9E9-1D3" was acquired from BioProbe BV (Amstelveen, The Netherlands), it is unclear if a cell line that produces an antibody having the exact structural and chemical identity of the antibody "B9E9" to which the claims 25 and 27 refer is known and publicly available, or can be reproducibly isolated without undue experimentation.

In addition, it is unclear if a cell line that produces an antibody having the exact structural and chemical identity of the antibody "B9E9" to which the claims 25 and 27 refer is known and publicly available, or can be reproducibly isolated without undue experimentation, because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies thereby, which may or may not have the same binding specificity.

Without access to a hybridoma cell line producing the antibody "B9E9" to which the claims refer, it would not be possible to practice the claimed invention, because it would not be possible to make the antibody. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

MPEP § 2404.01 states to avoid the need for a deposit, biological materials must be known and readily available – *neither concept alone suffices.*

Although the specification suggests that the hybridoma "B9E9-1D3" can be acquired from BioProbe BV (Amstelveen, The Netherlands), there is uncertainty as to whether the hybridoma produced by the hybridoma cell line disclosed in the Internet published catalog of BioProbe BV is the same as the antibody to which the claims refer. In addition, Applicant has failed to make of record any of the facts and circumstances surrounding the access to the biological materials from said company. MPEP § 2401.01 states: "The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean

that the deposited biological material is readily available". So, the fact that Applicant was able to obtain the materials in question from a given company prior to the filing date of the application does not establish that upon issuance of a patent on the application that such material would continue to be accessible to the public.

Applicant is invited to clarify the record by affirming that the antibody to which claims 25 and 27 are directed is the same as the anti-CD20 antibody produced by the hybridoma cell line "B9E9", which is commercially available from BioProbe BV (Bandung, Indonesia), as disclosed in the Internet published catalog of record.

Then, in accordance with MPEP § 2404.01, if Applicant can establish that a hybridoma producing the monoclonal antibodies "B9E9" is known and readily available, the Office will accept the showing.

MPEP § 2404.01 states:

> The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. See the final rule entitled "Deposit of Biological Materials for Patent Purposes," 54 FR 34864, 34875 (August 22, 1989).

However, it should be noted that MPEP § 2404.01 also states that, in such instances, Applicant will take the risk that the material may cease to be known and readily available; and such a defect cannot be cured by reissue after the grant of a patent.

In any event, and particularly if the monoclonal antibody or the hybridoma producing the monoclonal antibody is not commercially available, a suitable deposit for patent purposes is suggested, since the deposits would remedy this issue by satisfying the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809).

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is

necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 25, 27, and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25, 27, and 65 are indefinite because claims 25 and 27 use the laboratory designation "B9E9" as the sole means of identifying the antibody to which the claims are directed, particularly since, according to claim 18, the antibody can bind any one of a cell surface protein or cell-associated stromal matrix protein selected from the group consisting of CD20, CD45, EGP40, CEA, TAG72, NCAM, β-HCG, a mucin, and neoangiogenic antigens. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies produced thereby. Amending claims 25 and 27 to recite that the antibody binds CD20 and to include the depository accession number of the antibody or hybridoma producing the antibody can obviate this ground of rejection, because

deposit accession numbers are unique identifiers that unambiguously define a given hybridoma and/or monoclonal antibody.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 18-22, 24, 26, 28-32, 38, 39, and 65 rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,571,894 A (of record), as evidenced by Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), Kumar et al. (*Semin. Oncol.* **28**: 27-32, 2001), and US Patent No. 6,451,995 B1 (of record).

Claims 18-22 are drawn to a fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises at least 129 amino acids of streptavidin, wherein said second polypeptide is an antibody or antigen-binding fragment thereof that binds a neoangiogenic antigen and wherein said fusion protein is expressed as a soluble protein in the periplasmic space (claim 18), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20, respectively), or wherein said linker consists of between 4 and 20 amino acids (claim 21) or between 5 and 10 amino acids (claim 22). Claims 24, 26, 28-32, 38, and 39 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26), or wherein a linker connects the variable light and variable heavy chains of the single-chain antibody (claim 28), wherein the linker comprises at least 10, 15, or 20 amino acids (claims 29, 30, and 31, respectively), wherein the linker comprises at least four repeats of SEQ ID NO: 47 (claim 32), or wherein the first polypeptide comprises at least amino acids 25-182, 29-182, 38-174, 38-175, 38-175, 38-176, 38-177, 38-178, 38-179, 38-180, 38-181, or 38-182 of streptavidin, as set forth in SEQ ID NO: 2 (claim 38 and 39). Claim 65 is drawn to a

composition comprising such a fusion protein of any one of claims 18-22, 24, 26, 28-32, 38, and 39.

US Patent No. 5,571,894 A ('894) teaches a fusion protein comprising streptavidin from *Streptomyces avidinii*, which is capable of strongly binding biotin, and a single-chain antibody (scFv) that binds Her2/neu (encoded by *c-erbB-2*); see the entire document (e.g., the abstract; and column 3, lines 12-29). '894 teaches the fusion protein can be expressed as a soluble protein in the periplasm; see, e.g., column 32, lines 60-68; and column 33, lines 22-41. '894 teaches that streptavidin and the scFv can be adjoined by a linker (i.e., peptide spacer) of one or more amino acids, e.g., 1-10 amino acids; see, e.g., column 6, lines 18-20. '894 teaches the heavy and light chain variable domains of the scFv can be adjoined by a linker (i.e., peptide spacer) of about 10 to 30, e.g., around 15 amino acids; see, e.g., column 6, lines 1-17. '894 teaches the linker adjoining the heavy and light chain variable domains of the scFv can consist of repeats of the sequence "GGGGS", which is identical to the sequence set forth as SEQ ID NO: 47 in the instant application; see, e.g., column 29, lines 48-55. Because '894 teaches such a linker can consist of tandem repeats of the sequence "GGGGS" and that the linker can be about 10 to 30 amino acids in length, '894 teaches that the linker adjoining the heavy and light chain variable domains of the scFv can consist of up to six, or at least four repeats of SEQ ID NO: 47. '894 teaches compositions comprising the fusion protein; see, e.g., column 22, line 52, through column 23, line 4.

'894 teaches a fusion protein comprising streptavidin from *Streptomyces avidinii,* which is capable of strongly binding to biotin (column 3, lines 27-29), but does not teach the fusion protein is a "genomic streptavidin fusion protein" that comprises a first polypeptide comprising "at least 129 residues of streptavidin, as set forth in SEQ ID NO: 2" (claim 18). At page 6 (lines 12 and 13), the specification defines "genomic streptavidin", as used therein, as "a sequence comprising at least 129 residues of the sequence set forth in Figure 4 [i.e., SEQ ID NO: 2]". As evidenced by Database PIR 78 Accession No. A23513 (Exhibit I), streptavidin isolated from Streptomyces avidinii is a protein having an amino acid sequence of 183 amino acids that is identical to SEQ ID NO: 2. Accordingly, since the streptavidin molecule of the prior art is from *Streptomyces avidinii* and is capable of strongly binding biotin, the prior art appears to teach a fusion protein comprising a streptavidin molecule that is the same as "genomic streptavidin".

Therefore, absent a showing of any difference, the fusion protein of '894 comprising streptavidin from *Streptomyces avidinii,* which is capable of strongly binding to biotin, is deemed the same as the "genomic streptavidin fusion protein" of instant claims comprising a first polypeptide comprising "at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2", since it appears streptavidin molecule of the fusion protein of the prior art is identical to SEQ ID NO: 2. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion protein is different than that taught by the prior art.

Kumar et al. teaches that c-erbB-2 encodes the human epidermal growth factor receptor 2 (HER2), which is overexpressed or amplified in several human malignancies; see the entire document (e.g., the abstract). Kumar et al. teaches overexpression of HER2 in human tumor cells is closely associated with increased angiogenesis; see, e.g., the abstract. Therefore, absent a showing of any difference, the fusion protein of the prior art is deemed the same as the claimed fusion protein, since, as evidenced by Kumar et al., the growth factor receptor HER-2, which is encoded by *c-erbB-2*, is a "neoangiogenic antigen" closely associated with angiogenesis in neoplastic cells and tissues, such as malignant tumors. In further support of this interpretation of the claims, it is noted that, at page 3, line 30, the specification discloses the fusion protein can comprise a single-chain antibody that binds "her2/neu".

US Patent No. 6,451,995 B1 teaches a fusion protein comprising a streptavidin and a single-chain antibody is capable of forming a tetrameric complex with a second, third, and fourth fusion protein, as recited in claim 24; see the entire document (e.g., column 64, lines 8-13). Therefore, absent a showing of any difference, the fusion protein of the prior art is deemed the same as the claimed fusion protein, since, as evidenced by US Patent No. 6,451,995 B1, the fusion protein of the prior art is reasonably expected to be capable of forming a tetrameric complex with a second, third, and fourth fusion protein.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 18-22, 24, 26, 28-30, 38, 39, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez-Diez et al. (*Nucl. Med. Biol.* **23**: 459-466, 1996) in view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993) (of record) and WO 89/03422 A, as evidenced by Guan et al. (*Appl. Microbiol. Biotechnol.* **44**: 753-758, 1996) (of record).

Claims 18-22 are drawn to a fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises at least 129 amino acids of streptavidin, wherein said second polypeptide is an antibody or antigen-binding fragment thereof that binds TAG72, and wherein said fusion protein is expressed as a soluble protein in the periplasmic space (claims 18), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20, respectively), or wherein said linker consists of between 4 and 20 amino acids (claims 21) or between 5 and 10 amino acids (claim 22). Claims 24, 26, 28-30, 38, and 39 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26), or wherein a linker connects the variable light and variable heavy chains of the single-chain antibody (claim 28), wherein the linker comprises at least 10 or 15 amino acids (claims 29 and 30, respectively), or wherein the first polypeptide comprises at least amino acids 25-182, 29-182, 38-174, 38-175, 38-175, 38-176, 38-177, 38-178, 38-179, 38-180, 38-181, or 38-182 of streptavidin, as set forth in SEQ ID NO: 2 (claim 38 and 39). Claim 65 is drawn to a composition comprising such a fusion protein of any one of claims 18-22, 24, 26, 28-30, 38, and 39.

At page 24, lines 20-22, the specification discloses: "Accordingly, in one embodiment of the present invention, scFvSA is a conjugate (fusion) of the targeting moiety (scFv) and ligand

(streptavidin)". While such an embodiment might be produced by chemically conjugating an scFv and streptavidin, claim 18, as amended by the paper filed June 17, 2004, recites, "wherein said fusion protein is expressed as a soluble protein in the periplasmic space"; therefore, the claims are presently drawn to a fusion protein produced by recombinant DNA technology in bacteria, as opposed to a fusion protein produced by chemically conjugating its component proteins.

Alvarez-Diez et al. teaches a fusion protein for pretargeted tumor imaging in nude mice bearing subcutaneuous LS174T human colon cancer xenografts (abstract). The fusion protein is comprised of streptavidin chemically conjugated to anti-TAG72 monoclonal antibody CC49; see entire document, e.g., the abstract and page 460, column 1.

Alvarez-Diez et al. does not expressly teach such a fusion protein, which is produced by recombinant DNA technology as a soluble protein in the periplasmic space, wherein streptavidin and the antibody are separated by a linker of between 5 and 10 amino acids; nor does Alvarez-Diez et al. expressly teach substituting a single-chain Fv antibody fragment derived from monoclonal antibody CC49, which single-chain Fv antibody fragment comprises a linker connecting the light and heavy chain variable chains by at least 15 amino acid residues.

Goshorn et al. teaches a recombinant DNA method for preparing a fusion protein comprising an antibody and an enzyme for two-step pretargeting tumors for imaging or treatment; see entire document (e.g., the introduction). Goshorn et al. teaches chemical conjugates can be highly heterogenous due to the lack of specificity inherent in the cross-linking reagents used (page 2123, column 2). Goshorn et al. suggests there may be significant advantages in using recombinant methods for the preparation of antibody-enzyme conjugates, since uniform products are obtained that should have more predictable biological properties (page 2123, column 2). Goshorn et al. teaches a genetic construction encoding a fusion protein comprising an antibody and an enzyme, wherein the antibody and the enzyme are adjoined by a linker of six amino acids; see, e.g., page 2124, Figure 1. Goshorn et al. discloses the recombinant fusion protein binds tumor cells at least as well as the chemically conjugated fusion protein (abstract). Goshorn et al. discloses another advantage of genetically engineering fusion proteins, namely that the fusion proteins can be produced using prokaryotic expression systems, which grow rapidly and inexpensively (page 2126, column 2). In addition, Goshorn et al.

teaches single-chain Fv fragments of antibodies with desired specificity afford the opportunity of maintaining the antigen-binding characteristics of the multichain parental antibody on a single molecule that is a fraction of the molecular weight (page 2126, paragraph bridging columns 1 and 2). Goshorn et al. teaches single-chain antibody fragments have been shown to offer advantages over whole antibody with respect to tumor penetration and clearance from circulation (page 2126, column 2). Goshorn et al. teaches a single-chain antibody comprising a heavy and light chain linked by an amino acid sequence of 18 residues (page 2123, column 2).

WO 89/03422 A (Edwards) teaches a synthetic DNA molecule encoding a streptavidin molecule, which comprises an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 2 in the instant application; see entire document (e.g., Figure 2). Edwards discloses the DNA molecule can be used to produce a genetic construct encoding a fusion protein possessing biotin binding activity, which comprises the amino acid sequence of the streptavidin fused to the amino acid sequence of any other protein; see, e.g., page 4, paragraph 4.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the of the invention to produce a fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a scFv antibody having binding specificity for TAG72 by recombinant DNA technology, as opposed to chemical conjugation, using a DNA construct comprising the synthetic DNA molecule disclosed by WO 89/03422 A (Edwards) joined to a DNA molecule encoding the scFV, because Goshorn et al. teaches the necessary methodology and suggests that recombinant methodology offers advantages over chemical methodology, namely the production of more uniform products that should have more predictable biological properties and the capability of using prokaryotic expression systems, which grow rapidly and inexpensively. Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the of the invention to produce a scFv fragment of monoclonal antibody CC49, instead of the whole monoclonal antibody used by Alvarez-Diez et al., to produce a fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a scFv antibody having binding specificity for TAG72, because Goshorn et al. suggests the use of the scFv, rather than the monoclonal antibody, offer advantages over whole antibody with respect to tumor penetration and clearance from

circulation. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to study the potential of the fusion protein in imaging or treating tumors.

Guan et al. teaches that when the streptavidin gene from *S. avidinii* was expressed in *E. coli* as a non-fusion protein, the streptavidin protein accumulated primarily in inclusion bodies; but Guan et al. discloses that a fusion protein comprising streptavidin is expressed *as soluble protein* in *E. coli*; see the entire document (e.g., the abstract). Therefore, although neither Alvarez-Diez et al. nor Goshorn et al. suggest that a fusion protein comprising streptavidin and the single-chain antibody, which is produced by recombinant DNA technology in bacteria, is expressed as a soluble protein in the periplasm, absent a showing of any difference, said fusion protein is deemed the same as the fusion protein of claim 24. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein, which is expressed as a soluble fusion protein in the periplasm. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion protein is different than that taught or suggested by the prior art.

16. Claims 31, 32, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez-Diez et al. (*Nucl. Med. Biol.* **23**: 459-466, 1996) in view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993) (of record) and WO 89/03422 A, as evidenced by Guan et al. (*Appl. Microbiol. Biotechnol.* **44**: 753-758, 1996) (of record), as applied to claims 18-22, 24, 26, 28-30, 38, 39, and 65 above, in further view of Desplancq et al. (*Protein Engineering* **7**: 1027-1033, 1994) (of record).

Claims 31 and 32 are drawn to a fusion protein comprising a first polypeptide comprising at least 129 amino acids of SEQ ID NO: 2 and a single chain Fv fragment of monoclonal antibody that binds TAG72 comprising a light and heavy variable chain connected by a linker comprising at least 20 amino acid residues (claim 31), or more particularly by a linker comprising at least 4 repeats of SEQ ID NO: 47 (claim 32). Claim 65 is drawn to a composition comprising such a fusion protein of claim 31 or 32.

Alvarez-Diez et al., Goshorn et al., and WO 89/03422 A (Edwards) teach that which is set forth in the above rejection of claims 18-22, 24, 26, 28-30, 38, 39, and 65 under 35 U.S.C. 103(a).

Alvarez-Diez et al. does not expressly teach substituting a single-chain Fv antibody fragment comprising a linker of at least 20 amino acid residues connecting the light and heavy variable chains (claim 31) or comprising a linker of at least 4 repeats of SEQ ID NO: 47 (claim 32); and Goshorn et al. does not expressly teach or suggest a single-chain antibody having such a linker.

Similar to the teachings of Goshorn et al., Desplancq et al. teaches single-chain antibody fragments of an anti-TAG72 monoclonal antibody, but Desplancq et al. teaches such that are derived from an antibody designated B72.3, as opposed to CC49; see entire document (e.g., abstract). Desplancq et al. also teaches the Fv is the smallest antibody fragment that displays the monovalent antigen binding ability of the full-length parent antibody (page 1027, column 1). Desplancq et al. also teaches single-chain Fv antibody fragments are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical situations, notably for diagnosis of tumors (page 1027, column 1). Desplancq et al. teaches that single-chain Fv antibodies "are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical applications" (page 1027, column 1). In addition, Desplancq et al. teaches that the single-chain fragments of antibodies can be produced in which the variable light chain and the variable heavy chain of the single-chain fragment of antibody are adjoined by a linker comprising at least 20 amino acids, wherein said linker consists of at least four repeats of SEQ ID NO: 47, such that the resultant single-chain fragment of antibody is more soluble compared to one having a relatively shorter linker; see, e.g., the abstract. Desplancq et al. teaches that problems with precipitation, which are encountered during the manufacture of recombinant antibodies, might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody. Desplancq et al. teaches, "precipitation problems can be overcome by utilizing longer linkers", as their results showed that the tendency of the scFv variants to form dimers or higher molecular weight species decreases with increasing linker length (page 1033, column 1).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the of the invention to produce a fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a single chain Fv fragment of monoclonal antibody that binds TAG72 comprising a light and heavy variable chain connected by a linker comprising at least 4 repeats of SEQ ID NO: 47, since Desplancq et al. teaches a scFv antibody having the same binding specificity as the monoclonal antibody of Alvarez-Diez et al. and having a longer linker separating the variable heavy and light chains of the antibody than the linker of the scFv antibody suggested by the teachings of Goshorn et al. is more soluble and can overcome problems with precipitation that might be encountered during its manufacture. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to study the potential of the fusion protein in imaging or treating tumors.

17. Claims 18-21, 24, 26, 28-30, 37, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995) (of record) in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998) (of record), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996) (of record), and McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998) (of record), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995) (of record) and Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I).

Claims 18-21 and 37 are drawn to a fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises at least 129 amino acids of streptavidin, wherein said second polypeptide is an antibody or antigen-binding fragment thereof binds CD20, and wherein said fusion protein is expressed as a soluble protein in the periplasmic space (claims 18 and 37), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20, respectively) or consists of between 4 and 20 amino acids (claims 21). Claims 24, 26, and 28-30 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26) comprising a linker connecting the variable light and variable heavy chains

(claim 28), wherein the linker comprises at least 10 or 15 amino acids (claims 29 and 30, respectively). Claim 65 is drawn to a composition comprising such a fusion protein of any one of claims 18-21, 24, 26, 28-30, and 37.

Dubel et al. teaches a fusion protein, and a composition thereof, comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises a portion of genomic streptavidin and wherein said second polypeptide is an antibody or antigen-binding fragment thereof, wherein said first and second polypeptides are separated by a linker consisting of 5 amino acids; see the entire document. Dubel et al. teaches the fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein. The fusion protein of Dubel et al. comprises a single-chain Fv antibody fragment in which a linker connects the variable light and variable heavy chains. As evidenced by Kipriyanov et al., the linker connecting the variable light and variable heavy chains consists of 15 amino acids. In addition, Dubel et al. teaches that single-chain Fv antibodies (scFv) "represent potentially very useful molecules for the targeted delivery of drugs, toxins, or radionuclides to a tumour site" (page 201, column 2). Dubel et al. discloses, "various heterologous protein moieties can also be genetically fused to scFv antibodies to generate bifunctional fusion proteins" (page 202, column 1). Additionally, Dubel et al. teaches that streptavidin "exhibits one of the strongest noncovalent binding affinities known for a biomolecule", namely biotin (page 208, column 1). Dubel et al. teaches that the fusion protein comprising a single-chain antibody and streptavidin might be "usefully employed for the in vitro purging of autologous bone marrow transplants to eliminate B lymphocytes in the treatment of leukemias and malignant lymphomas" (page 208, column 1).

The single-chain antibody of the fusion protein of Dubel et al. is derived from a monoclonal antibody that binds the "215" epitope of *D. melanogaster* RNA polymerase II; however, Dubel et al. does not teach a fusion protein comprising an antibody that binds specifically to CD20.

The first polypeptide of the fusion protein of Dubel et al. consists of 126 amino acids of streptavidin; however, Dubel et al. does not expressly teach that the first polypeptide of the fusion protein can comprise at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2.

McLaughlin et al. teaches that CD20 is an appealing target for a therapeutic antibody, because it is expressed on B cells, and progenitors thereof, from the pre-B cell stage to the activated B cell stage, but not on stem cells, normal plasma cells, or cells of other lineages; see the entire document (e.g., page 1763, columns 2 and 3). McLaughlin et al. discloses that CD20 is expressed on most B cell lymphomas and chronic lymphocytic leukemias and on 50% of pre-B cell acute lymphoblastic leukemias (page 1763, column 3). McLaughlin et al. teaches the clinical status and optimal use of Rituximab™, a recombinant humanized monoclonal antibody that specifically binds CD20 (abstract). Mclaughlin et al. discloses, "as the first MoAb [monoclonal antibody] to gain FDA approval for the treatment of a malignancy, rituximab signals the beginning of a promising new era in cancer therapy" (abstract). McLaughlin et al. teaches the chimeric antibody inhibits the growth of cancer cells expressing CD20 by a mechanism involving complement-dependent cytotoxicity. McLaughlin et al. also discloses that the antibody sensitizes cancer cells to the cytotoxic effects of drugs and toxins; see, e.g., page 1764, column 3.

Ohno et al. teaches that tissue-specific delivery of a variety of molecules is a valuable technique for medical research; see the entire document, e.g., the abstract. Ohno et al. discloses, "the cell-targeting moiety can be either antibodies or protein ligands (growth factors) that recognize the corresponding antigens or receptor (page 401, column 1). Ohno et al. demonstrates a streptavidin-ligand fusion protein, ST-TGF-α, can efficiently target biotinylated protein to cells that express the ligand's receptor (abstract). Ohno et al. teaches that streptavidin-ligand and streptavidin-antibody fusion proteins have a number or advantages over immunotoxins and recombinant toxins for treatment of disease, namely cancer; see, e.g., page 401, columns 1 and 2; and page 404, columns 1 and 2). Ohno et al. discloses: "Because biotin can be easily incorporated into a wide range of macromolecules without interfering with biological activities (Wilchek and Bayer, 1990) steptavidin containing-proteins such as ST-TGF-α have wider applicability as bridges to deliver specific molecules such as toxins" (page 405, column 1). Then, Ohno et al. teaches, "other chimeric molecules in which the TGF-α moiety has been replaced by an alternate targeting element may have equally broad applicability to targeting a variety of cell types with equal affinities" (page 405, column 2).

Gallizia et al. teaches a fusion protein comprising residues 15 to 159 of streptavidin, which is expressed in *E. coli* as a soluble protein; see the entire document (e.g., the abstract; and page 196, column 1). Gallizia et al. discloses that streptavidin is generally expressed in *E. coli* as an insoluble protein (abstract); therefore, Gallizia et al. teaches that a recombinant streptavidin molecule in which the first N-terminal residues are substituted with the T7-tag peptide can be used advantageously, because it can be produced in *E. coli* as a soluble and functional protein, which can be purified in two simple steps with yields of 70 mg per liter of culture; see, e.g., the abstract. Gallizia et al. teaches the recombinant fusion protein and natural streptavidin bind biotin with very similar affinity; see, e.g., page 196, column 1. Gallizia et al. teaches the biotin binding characteristics of the recombinant fusion protein are consistent with that which would be expected for a tetravalent structure, which suggests that a molecule of the fusion protein is capable of forming a tetrameric complex with a second, third, and fourth molecule of the fusion protein (page 195, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Dubel et al. to produce a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is single-chain Fv antibody that binds CD20. One of ordinary skill in the art would have appreciated the fact that, based upon the teachings of Dubel et al., McLaughlin et al., and Ohno et al., the fusion of such an antigen-binding fragment and streptavidin could be used simultaneously to inhibit the growth of cancer cells expressing CD20 by a mechanism involving complement-dependent cytotoxicity and to selectively and specifically target biotin-conjugated drugs, toxins, or radionuclides to a CD20+ lymphoma tumor cell, because McLaughlin et al. teaches that anti-CD20 antibody-directed therapy can be used effectively to treat patients diagnosed with lymphoma, because Dubel et al. and Ohno et al. teach or suggest the utility of targeting drugs, toxins, or radionuclides to cancer cells using single-chain antibody fusion proteins comprising streptavidin, and finally because McLaughlin et al. teaches that an anti-CD20 antibody can sensitize cancer cells to the cytotoxic effects of drugs and toxins. One of ordinary skill in the art would have been motivated have modified the fusion protein of Dubel et al. in this manner to treat lymphoma, for example.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have replaced core streptavidin of the fusion protein of Dubel et al. with the recombinant streptavidin molecule of Gallizia et al., because Gallizia et al. discloses a recombinant streptavidin molecule in which the first N-terminal residues are substituted with the T7-tag peptide can be used advantageously, since it can be produced in *E. coli* as a soluble and functional protein. One of ordinary skill in the art at the time the invention was made would have been motivated to make the replacement because the teachings of Gallizia et al. suggest that the making the replacement would be advantageous.

Gallizia et al. teaches a cDNA molecule encoding amino acids 15-159 of "mature streptavidin" from *Streptomyces avidinii,* which is capable of strongly binding to biotin (see, e.g., page 193, column 2, and page 195, Figure 3); however, Gallizia et al. does not disclose the amino acid sequence of the streptavidin molecule. As evidenced by Database PIR 78 Accession No. A23513 (Exhibit I), streptavidin isolated from Streptomyces avidinii is a protein having an amino acid sequence of 183 amino acids that is identical to SEQ ID NO: 2. Since the streptavidin molecule of the prior art is from *Streptomyces avidinii,* comprises amino acids 15 to 159 of "mature streptavidin", and is capable of strongly binding biotin, the prior art appears to teach a streptavidin molecule that is the same as "genomic streptavidin", which at page 6 the specification defines as a polypeptide comprising at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2. Therefore, absent a showing of any difference, the fusion protein of the prior art, which comprises a streptavidin molecule according to Gallizia et al., is deemed the same as the "genomic streptavidin fusion protein" of instant claims. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. For example, the Office does not have the facilities to produce the streptavidin encoded by the cDNA molecule of Gallizia et al. to determine if the molecule comprises at least 129 amino acids of the amino acid sequence set forth as SEQ ID NO: 2 and is, otherwise, distinct from the claimed "genomic streptavidin fusion protein". In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion protein is different than that taught by the prior art.

18. Claims 22 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995) (of record) in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998) (of record), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996) (of record), and McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998) (of record), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995) (of record) and Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), as applied to claims 18-21, 24, 26, 28-30, 37, and 65 above, and in further view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993) (of record).

Claim 22 is drawn to the fusion protein of claim 21, wherein said linker is between 5 and ten amino acids (i.e., 6-9 amino acids). Claim 65 is drawn to a composition comprising such a fusion protein of claim 22.

Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. teach that which is set forth above.

The first and second polypeptides of the fusion protein of Dubel et al. are adjoined by a linker, which consists of 5 amino acids, and the first and second polypeptides of the fusion protein of Gallizia et al. are not separated by a linker.

However, none of Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. expressly teach that a fusion protein can comprise a first and second polypeptide adjoined by a linker of between 5 and 10 amino acids.

Goshorn et al. teaches that which is set forth above; in particular, Goshorn et al. teaches a fusion protein comprising a first and second polypeptide, which are joined by a linker of 6 amino acids.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dubel et al. to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first and second polypeptides are separated by a linker that is 6 amino acids, because Goshorn et al. teaches a fusion protein comprising a first and a second polypeptide adjoined by a linker of 6 amino acids, which retains the ability to bind specifically to the antigen to which the antibody from the which the fusion protein is derived binds and retains the ability to bind specifically to the substrate to

which the second polypeptide from which the fusion protein is derived binds. One of ordinary skill in the art at the time the invention was made would have recognized the equivalency of a linker consisting of 5 amino acids and a linker consisting of 6 amino acids, because the prior art teaches that either a linker consisting of 5 amino acids or a linker consisting of 6 amino acids is suitable for use in the fusion protein. See MPEP §§ 2144.06 and 2144.07.

19. Claims 31, 32, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995) (of record) in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998) (of record), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996) (of record), and McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998) (of record), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995) (of record) and Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), as applied to claims 18-21, 24, 26, 28-30, 37, and 65 above, and in further view of Desplancq et al. (*Protein Engineering* **7**: 1027-1033, 1994) (of record).

Claims 31 and 32 are drawn to a fusion protein comprising a first polypeptide comprising at least 129 amino acids of SEQ ID NO: 2 and a single chain Fv fragment of monoclonal antibody that binds TAG72 comprising a light and heavy variable chain connected by a linker comprising at least 20 amino acid residues (claim 31), or more particularly by a linker comprising at least 4 repeats of SEQ ID NO: 47 (claim 32). Claim 65 is drawn to a composition comprising such a fusion protein of claim 31 or 32.

Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. teach that which is set forth in the rejection above.

The linker adjoining the variable light chain and the variable heavy chain of the single-chain antibody of the fusion protein of Dubel et al. consists of 15 amino acids.

However, none of Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. expressly teach that the fusion protein can comprise an antibody or antigen-binding fragment thereof, wherein said antibody is a single-chain Fv fragment comprising a variable light chain and the variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47.

Desplancq et al. teaches that which is set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Dubel et al. to produce a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is single-chain Fv antibody comprising a variable light chain and a variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, because Desplancq et al. teaches that single-chain antibodies can be produced in which the variable light chain and the variable heavy chain of the single-chain antibody is adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, such that the resultant antibody is more soluble compared to an antibody having a relatively shorter linker. One of ordinary skill in the art would have been motivated at the time the invention was made to separate the variable heavy and light chains of the single-chain Fv antibody by a linker consisting of at least four gly-gly-gly-gly-ser (SEQ ID NO: 47) linkers, because Desplancq et al. teaches that problems with precipitation, which are encountered during the manufacture of recombinant antibodies, might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody.

Double Patenting

20. The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 18-22, 24, 26, 28-32, 37-39, and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-24, 26, 27, 29-38, 40-42, and 79-81 of co-pending Application No. 10/013,173. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reason set forth in the previous Office action mailed December 17, 2003.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 10 of the amendment filed June 17, 2004, Applicant has requested that this issue be held in abeyance until allowable subject matter is identified.

Conclusion

22. No claims are allowed.

23. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Milenic et al. (*Cancer Res.* **51**: 6363-6371, 1991) teaches the construction of a recombinant single-chain Fv of the anti-TAG72 monoclonal antibody CC49.

24. This Office action has an attached requirement for information under 37 CFR § 1.105. A complete reply to this Office action must include a complete reply to the attached requirement for information. The time period for reply to the attached requirement coincides with the time period for reply to this Office action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
September 15, 2004

Jeffrey Siew
JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
9/17/04

Requirement for Information under 37 CFR § 1.105

1. Applicant and the assignee of this application are required under 37 CFR § 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application. See MPEP §§ 704.10 [R-2] and 704.11.

2. In response to this requirement, please provide the title, citation and copy of each publication that any of the applicants relied upon to develop the disclosed subject matter that describes the applicant's invention, in particular that which was relied upon to develop the "B9E9 scFvSA Fusions" described at pages 31 and 32 in Example II. Moreover, please provide the title, citation and copy of each publication (e.g., a catalog published by Bioprobe BV (Amstelveen, The Netherlands) listing the commercial availability of the antibody B9E9 or the hybridoma producing the antibody) that any of the applicants relied upon to draft the subject matter of claims 25 and 27. For each publication, please provide a concise explanation of the reliance placed on that publication in the development of the disclosed subject matter.

Since according to the disclosure the hybridoma B9E9-1D3 was acquired by Applicant from "Bioprobe BV (Amstelveen, The Netherlands)", this requirement for information is made to determine whether the specification's disclosure at page 31 (particularly, lines 9 and 10) describing the antibody B9E9 and the hybridoma, which produces the antibody, as being known or conventional, may be considered as an admission of prior art, since the information is unfamiliar to examiner and cannot be found within the application file or from the examiner's search of the prior art. The request for further details of the information disclosed by Applicant would be thus be relevant to the question of patentability and serve to identify products and services in the prior art embodying the disclosed subject matter.

3. In responding to those requirements that require copies of documents, where the document is a bound text or a single article over 50 pages, the requirement may be met by providing copies of those pages that provide the particular subject matter indicated in the requirement, or where such subject matter is not indicated, the subject matter found in applicant's disclosure.

4. The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

5. The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained will be accepted as a complete reply to the requirement for that item.

6. This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: July 12, 2004, 11:48:34 ; Search time 20 Seconds
(without alignments)
880.152 Million cell updates/sec

Title: US-09-589-870B-2
Perfect score: 936
Sequence: 1 MRKIVVAAIAVSLTTVSITA.....IDAAKKAGVNNGNPLDAVQQ 183

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 283366 seqs, 96191526 residues

Total number of hits satisfying chosen parameters: 283366

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : PIR_78:*
1: pir1:*
2: pir2:*
3: pir3:*
4: pir4:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	936	100.0	183	2	A23513	streptavidin precu
2	932	99.6	183	2	S57284	streptavidin v1 pr
3	897	95.8	183	2	S57285	streptavidin v2 pr
4	146.5	15.7	150	2	S42204	avidin-related pro
5	143.5	15.3	152	1	VICH	avidin precursor (
6	121.5	13.0	150	2	S42201	avidin-related pro
7	120.5	12.9	150	2	S42203	avidin-related pro
8	120	12.8	1064	2	A40136	fibropellin Ia - s
9	116.5	12.4	150	2	S42202	avidin-related pro
10	112	12.0	595	2	A48658	flagellin - Escher
11	102	10.9	1310	2	AD1380	glycosidase homolo
12	102	10.9	1374	2	AE3259	extracellular seri
13	101	10.8	595	2	B48658	flagellin - Escher
14	100.5	10.7	1026	2	A48995	paracrystalline su
15	100.5	10.7	1073	2	C87374	S-layer protein Rs
16	99.5	10.6	1477	2	B43855	high-molecular-wei
17	99.5	10.6	2468	2	A83412	hypothetical prote
18	96.5	10.3	741	2	F70722	probable glcB prot
19	96	10.3	4776	2	E95206	cell wall surface
20	94.5	10.1	507	2	T35677	probable hydrolase
21	94	10.0	570	2	S56132	cellulase (EC 3.2.
22	94	10.0	967	2	S66852	hypothetical prote
23	93	9.9	1225	1	B64234	hypothetical prote
24	92.5	9.9	1018	2	H83135	probable adhesin P
25	92.5	9.9	1461	2	E90696	hypothetical prote
26	92.5	9.9	1461	2	A85547	hypothetical prote
27	92	9.8	1217	2	S52714	sericin1B - silkwo
28	91.5	9.8	1063	2	D86731	hypothetical prote
29	91.5	9.8	1122	2	G64887	probable tail fibe
30	91.5	9.8	2249	2	A41477	190K surface antig
31	91	9.7	782	2	AI0062	conserved hypothet
32	91	9.7	867	2	T45463	membrane glycoprot
33	91	9.7	1035	2	AD3203	autotransporter pr
34	90.5	9.7	2761	2	T21064	hypothetical prote
35	90	9.6	13288	2	T03099	mucin, submaxillar
36	89.5	9.6	971	2	B90835	probable tail fibe
37	89.5	9.6	973	2	C85693	probable membrane
38	89	9.5	255	1	CPSMMU	muramoylpentapepti
39	89	9.5	488	2	A32235	poly(3-hydroxybuty
40	89	9.5	641	2	AI2524	hypothetical prote
41	89	9.5	866	2	T45462	membrane glycoprot
42	89	9.5	1999	2	AB2018	hypothetical prote
43	88.5	9.5	131	2	AI1540	hypothetical prote
44	88.5	9.5	447	2	C84306	hypothetical prote
45	88.5	9.5	465	2	A47023	S-layer protein -

ALIGNMENTS

RESULT 1
A23513
streptavidin precursor - Streptomyces avidinii
C;Species: Streptomyces avidinii
C;Date: 03-Nov-1987 #sequence_revision 03-Nov-1987 #text_change 11-Jan-2002
C;Accession: A23513; S11540
R;Argarana, C.E.; Kuntz, I.D.; Birken, S.; Axel, R.; Cantor, C.R.
Nucleic Acids Res. 14, 1871-1882, 1986
A;Title: Molecular cloning and nucleotide sequence of the streptavidin gene.
A;Reference number: A23513; MUID:86148514; PMID:3951999
A;Accession: A23513
A;Status: preliminary
A;Molecule type: DNA
A;Residues: 1-183 <ARG>
A;Cross-references: GB:X03591; NID:g46740; PIDN:CAA27265.1; PID:g46741
R;Gitlin, G.; Bayer, E.A.; Wilchek, M.
Biochem. J. 269, 527-530, 1990
A;Title: Studies on the biotin-binding sites of avidin and streptavidin. Tyrosine resi
A;Reference number: S11540; MUID:90351377; PMID:2386489
A;Accession: S11540
A;Molecule type: protein
A;Residues: 54-66,'X',68 <GIT>
C;Superfamily: streptavidin
C;Keywords: biotin binding; homotetramer
F;1-24/Domain: signal sequence #status predicted <SIG>
F;25-183/Product: streptavidin #status predicted <MAT>
F;67/Binding site: biotin (Tyr) #status predicted
F;78/Binding site: biotin (Tyr) #status predicted

Query Match 100.0%; Score 936; DB 2; Length 183;
Best Local Similarity 100.0%; Pred. No. 1.6e-66;
Matches 183; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 MRKIVVAAIAVSLTTVSITASASADPSKDSKAQVSAAEAGITGTWYNQLGSTFIVTAGAD 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MRKIVVAAIAVSLTTVSITASASADPSKDSKAQVSAAEAGITGTWYNQLGSTFIVTAGAD 60

Qy         61 GALTGTYESAVGNAESRYVLTGRYDSAPATDGSGTALGWTVAWKNNYRNAHSATTWSGQY 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GALTGTYESAVGNAESRYVLTGRYDSAPATDGSGTALGWTVAWKNNYRNAHSATTWSGQY 120

Qy        121 VGGAEARINTQWLLTSGTTEANAWKSTLVGHDTFTKVKPSAASIDAAKKAGVNNGNPLDA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 VGGAEARINTQWLLTSGTTEANAWKSTLVGHDTFTKVKPSAASIDAAKKAGVNNGNPLDA 180

Qy        181 VQQ 183
              |||
Db        181 VQQ 183
```

RESULT 2
S57284

Notice to Comply	Application No.	Applicant(s)	
	09/589,870	GOSHORN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency, Applicant should submit substitute copies of the sequence listing and the statement, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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For CRF Submission Help, call (703) 308-4212
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